Streptococcus pneumoniae-associated hemolytic uremic syndrome: More than just neuraminidase

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No conflicts of interest to declare
Healthy 3 year old girl presented to PCP with a 3 day history of fever (103°F) and non-productive cough, presumed viral illness. She remained febrile and was seen in local ED with fever, dehydration and new bilateral pleural effusions. She was admitted, started on Abx (rocephin) and hydration. She was transferred to UM the following day with decreasing renal and respiratory function. On arrival to UM, she was in respiratory distress with ↑O₂ requirements, increased pleural effusions, acute renal failure, anemia and thrombocytopenia. She was admitted to PICU.
UM Admission

On arrival, patient was febrile with nasal flaring and retractions and was ultimately intubated. She was anuric with fluid retention (↑3 kg/48 hrs).

Laboratory Studies:

CBC

Smear: > 3 shistocytes/hpf

Haptoglobin=18, LDH=2900

PT/PTT: WNL, ↑ fibrinogen=704

Electrolytes: BUN=54, Crt=2.0 → 2.9

Blood Cx: *S. pneumoniae*

Blood Bank
O+, screen neg
DAT: Polyspecific=2+
IgGw, C3=2+
Eluate: negative
Lectins: not requested
UM Course

She was intubated, started on vancomycin and zoysn, then transitioned to ampicillin after 48 hours. She had bilateral chest tubes placed. She was diagnosed with Strep-associated HUS and treated with one course TPE on UM-Day 2 by pediatrics nephrology to “remove neuraminidase and anti-T antibodies”, followed by CRRT. Her first 10 days were complicated by significant hypertension, pericarditis and persistent fevers. She received a few transfusions (4 PLTs, 5 RBC; unwashed) without complications or evidence of hemolysis. Infectious disease and pediatric surgery consulted on day +10.
XRAY: Day +10
CT Scan: Loculated Fluid Collection

Day +11

4.2 x 3.7 x 3 loculated cavitory lesion inferior to the heart
UM Course

Decision to pursue antibiotic treatment only. She continued to improve, requiring intermittent hemodialysis until discharge on UM-Day +30. Over the next 2 months she was hospitalized twice for acute cholecystitis s/p cholesteectomy for pigment stones and line-related sepsis. She is currently followed for stage III chronic renal failure (last Crt 1.2).
Platelet Count

Dialysis

TPE-1BV
albumin

3 Plt Tx
1 PLT (~15mL/kg)
(50 ml/kg!)
Chest tubes, lines
Hct and LDH

RBC Transfusions

Hct

LDH

TPE
Streptococcus-associated HUS

Invasive Pneumoccal Disease (CDC):
Isolation of *S. pneumoniae* from any sterile body site

Risk Factors:
- Age < 2 years or > 65 years
- Functional or anatomic asplenia
- Immune compromise
- Chronic heart, liver, lung or kidney disease

*SP-HUS is Rare Complication: 0.04-0.06% of IPD cases*
## Review Literature

### 6 Retrospective Registry-Type Reviews
- 124 patients
- 4 countries, 47 years total observation

### Smaller Case Series
- 20 patients, 5 countries

<table>
<thead>
<tr>
<th>Study</th>
<th>year</th>
<th>country</th>
<th>hospital</th>
<th>start</th>
<th>stop</th>
<th># years</th>
<th>No. pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang</td>
<td>2006</td>
<td>Tiawan</td>
<td>Chang Gung</td>
<td>1/1/2000</td>
<td>6/2005</td>
<td>4.5</td>
<td>7</td>
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<tr>
<td>Waters</td>
<td>2007</td>
<td>UK</td>
<td>7</td>
<td>1/1/1998</td>
<td>12/2005</td>
<td>7</td>
<td>43</td>
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<tr>
<td>Banerjee</td>
<td>2011</td>
<td>USA</td>
<td>11</td>
<td>1/1/1997</td>
<td>12/2009</td>
<td>12</td>
<td>37</td>
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</table>
## Patient Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th># Study</th>
<th># Pts</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>11</td>
<td>144</td>
<td>22 mo.</td>
<td>(3-56)</td>
</tr>
<tr>
<td>Sex</td>
<td>10</td>
<td>121</td>
<td>56% M, 43% F</td>
<td></td>
</tr>
<tr>
<td>Risk Factors</td>
<td>11</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevnar</td>
<td>2</td>
<td>48</td>
<td></td>
<td>(0, 76%)</td>
</tr>
</tbody>
</table>
## Clinical Presentation

<table>
<thead>
<tr>
<th>Clinical Dx</th>
<th>% Patients</th>
<th>Study Ranges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>80%</td>
<td>20-100%</td>
</tr>
<tr>
<td>Meningitis</td>
<td>19%</td>
<td>0-80%</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>64%</td>
<td>43-79%</td>
</tr>
<tr>
<td>Empyema</td>
<td>58%</td>
<td>9-100%</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>45%</td>
<td>9-71%</td>
</tr>
<tr>
<td>CNS complications*</td>
<td>24%</td>
<td>0-40%</td>
</tr>
</tbody>
</table>

*Seizures, intracranial hemorrhage, hydrocephalus, ↑ intracranial pressure
# Laboratory Studies

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Study Ranges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset HUS</td>
<td>6.5 days</td>
<td>5-14 days</td>
</tr>
<tr>
<td>Hgb (g/dL, nadir)</td>
<td>5.6</td>
<td>2.0-&gt;</td>
</tr>
<tr>
<td>PLT (K/μL, nadir)</td>
<td>25.6</td>
<td>4-127</td>
</tr>
<tr>
<td>ADAMTS13 (6 pts)</td>
<td>24%</td>
<td>5 – 44%</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>6100</td>
<td>1729-12,290</td>
</tr>
<tr>
<td>Peak Crt (uM/L)</td>
<td>3.7</td>
<td>2.5 - 4</td>
</tr>
<tr>
<td>Serology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“T-activated”</td>
<td>95%</td>
<td>80-100</td>
</tr>
<tr>
<td>DAT+</td>
<td>54%</td>
<td>0-100</td>
</tr>
</tbody>
</table>

ASFA 2015
<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Study Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU Admission</td>
<td>&gt;90%</td>
<td>86-95%</td>
</tr>
<tr>
<td>ICU LOS (n=2)</td>
<td>17 days</td>
<td>1-44 days</td>
</tr>
<tr>
<td>Hospital LOS</td>
<td>31</td>
<td>3-103 days</td>
</tr>
<tr>
<td>Ventilator (n=3)</td>
<td>67%</td>
<td>57, 59, 86%</td>
</tr>
<tr>
<td>Dialysis</td>
<td>87%</td>
<td>80-100%</td>
</tr>
<tr>
<td>TPE (n=3)</td>
<td>17% (9/53)</td>
<td>0 - 40%</td>
</tr>
<tr>
<td>Transfusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC</td>
<td>90%</td>
<td>57-100%</td>
</tr>
<tr>
<td>PLT</td>
<td>80%</td>
<td>40-100%</td>
</tr>
</tbody>
</table>
## Clinical Outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Study Ranges</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRF/ESRD</td>
<td>11%</td>
<td>0-33%</td>
</tr>
<tr>
<td>Renal Txp</td>
<td>&lt;3%</td>
<td>0-10%</td>
</tr>
<tr>
<td>CNS sequelae</td>
<td>~7%</td>
<td>0-27%</td>
</tr>
<tr>
<td>Death</td>
<td>14.6%</td>
<td>0-50%</td>
</tr>
<tr>
<td>Study</td>
<td>Meningitis</td>
<td>Dead</td>
</tr>
<tr>
<td>------------------</td>
<td>------------</td>
<td>------</td>
</tr>
<tr>
<td>Waters,2007</td>
<td>13</td>
<td>3 (23%)</td>
</tr>
<tr>
<td>Banerjee,2011</td>
<td>4</td>
<td>1 (25%)</td>
</tr>
<tr>
<td>Cabrera,1998</td>
<td>2</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>Erickson,1994</td>
<td>2</td>
<td>2 (100%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>25</strong></td>
<td><strong>8 (32%)</strong></td>
</tr>
</tbody>
</table>

* 4 pts = sensineural hearing loss
† 7 pts = “severe neurologic deficits”
‡ 1 pt = seizures, global developmental disorder
‡ 1 pt = multiple CVA, severe cognitive and motor deficits

80% Patients
Mortality in SP-HUS

- 2-fold higher with meningitis > pneumonia
- Meningitis -> 38% of all deaths
  - OR 3.5 (95% CI: 1.2 – 9.8)

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>115</td>
<td>17 (14.7%)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>25</td>
<td>8 (32%)</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>0.01</td>
</tr>
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</table>
### S. pneumoniae Virulence Factors

<table>
<thead>
<tr>
<th>Virulence Factor</th>
<th>Gene</th>
<th>MW</th>
<th>Location</th>
<th>Role in Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuraminidase</td>
<td>nanA (NanB, C)</td>
<td>108 kD</td>
<td>Cell Wall</td>
<td>Bacterial adherence, Sialidase</td>
</tr>
<tr>
<td>Pneumolysin</td>
<td>ply</td>
<td>53 kD</td>
<td>Cytoplasmic</td>
<td>Cytotoxin, cell lysis, Tissue Invasion, Immune suppression</td>
</tr>
<tr>
<td>Autolysin</td>
<td>lytA</td>
<td>36 kD</td>
<td>Cytoplasmic</td>
<td>Bacterial lysis, Release pneumolysin &amp; other proteins</td>
</tr>
<tr>
<td>Hyaluronate Lyase</td>
<td>hyl</td>
<td>107 kD</td>
<td>Cell Wall</td>
<td>Tissue Invasion, Digest extracellular matrix (ECM)</td>
</tr>
<tr>
<td>Pneumococcal surface protein A</td>
<td>pspA</td>
<td>~99 kD</td>
<td>Cell Wall</td>
<td>Inhibit C1q deposition, Immune evasion</td>
</tr>
<tr>
<td>PSP-C</td>
<td>pspC</td>
<td>59-105 kD</td>
<td>Cell Wall</td>
<td>Factor H binding, C4bBP binding, Immune evasion</td>
</tr>
</tbody>
</table>
S. pneumoniae neuraminidase

Product *nanA* gene
100% strains
Strain variation

Virulence Factor
NeuAc$\alpha$$2$-$3$ Gal
NeuAc$\alpha$$2$-$6$ Gal
NeuAc$\alpha$$2$-$6$ GalNAc
Glycoproteins, glycolipids

Hsiao et al. 2009
Biochem Biophys Res Comm 380:467-71
"T-activation"
Polyagglutinable RBC phenotype
Neo-expression of T-antigen (Thomsen-Friedenreich Antigen)

Lectin PNA

T-antigen

NeuAcα2 → 3 Galβ1 → 3GalNAc

O-Ser/Thr

Sialidase nanA

NeuAcα2→6

GYP A

O-glycans
PNA Hemagglutination

PNA versus MAA Hemagglutination

70% loss Sialic Acid

Adapted from Roziers et al, Transfusion 2014
T-Activation Caveats

Not specific for *S. pneumoniae*
- Clostridium, influenza, G- organisms

Not specific for HUS
- 43%-60% Invasive pneumoccal disease
- 67%-100% *S. pneumoniae*-associated anemia

Not specific to RBC glycans
- Platelets (GPIb), kidney, endothelium, WBC
- Desialylation of N-glycans, glycolipids
Figure 2. A: Kidney biopsy of our case: Peripheral glomerular capillary loops show positive fluorescence with anti-T lectin. B: Kidney biopsy of our case: Tubular epithelium shows positive fluorescence with anti-T lectin. C: Kidney biopsy of a patient with minimal change: Peripheral glomerular capillary loops show negative fluorescence with anti-T lectin. D: Kidney biopsy of a patient with HUS by Shiga-like toxin-producing *Escherichia coli* O157:H7: Peripheral glomerular capillary loops show negative fluorescence with anti-T lectin.

Shimizu et al. Clinical Nephrology 2012;78:328-331
**T-activation and HUS**

*Historically* believed to be driven by anti-T antibodies

- Pre-formed, naturally-occurring IgM antibodies (like ABO)
- Antibody-mediated complement activation

---

Other hypothesized roles

Loss of Factor H binding to sialic acids on cell membranes
↓ complement inhibition
↓ Risk tissue damage

T-activated cells bind galectin receptors on endothelium

CFH

Galectin-3
Is anti-T really the culprit?

**Anti-T Properties**

- Generally low titer
  - No correlation between titer, hemolysis
- Cold, low thermal amplitude
- Not fix complement in vitro

*S. pneumoniae* (IPD infections)

- T-activation common
- SP-HUS uncommon
**nanA required for T-activation**

Exposure of T-antigen in *S. pneumoniae* infection is dependent on neuraminidase A. Coats MT et al, Microbial Pathogenesis 2011;50:343-349.

**S. pneumoniae**

10^7 CFU

CBA/N mice

T-activation

1) RBC
2) Kidney

**Questions:**

1) *nanA* required?
2) Bacterial load
3) Impact antibiotics

NanA+ strains
NanA- strains
Coats et al: Microbial Pathogenesis 2011

<table>
<thead>
<tr>
<th>Bacteremia (CFU/mL)</th>
<th>nanA+</th>
<th>nanA-</th>
<th>Ringers</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1000</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>&lt;1000</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

nanA-, Ringer’s control

Kidney

nanA+

No investigation re: renal function, MAHA, HUS
Anti-T and RBC survival

No difference in RBC survival in mice by anti-T

Adapted or from Pettet et al, Mech Age Devel 1980;12:53-63
Thrombocytopenia due to nanA-dependent PLT desialylation and hepatic Ashwell Receptor

The Ashwell receptor mitigates the lethal coagulopathy of sepsis
Prabhjit K Grewal, Satoshi Uchiyama, David Ditto, Nissi Varki, Dzung T Le, Victor Nizet & Jamey D Marti
doi:10.1038/nm1760

Gal Epitopes

PLT count

PLT survival Asgr-null

RCA (Gal)
Pneumolysin (Ply)

Outer-membrane protein
Cholesterol-dependent cytolysin

Loss membrane integrity

Ply

Lipid

EM of Ply Pore

Shewell et al, PNAS 2014;epub E5312
Sonnen et al, Open Biology 2014;4:e14004
http://principlesofproteinstructure.blogspot.com
Pneumolysin induce RBC hemolysis

Ply binding to O RBC

Ply-induced hemolysis

Shewell PNAS 2014;111:E5312
Complement Activation & Consumption

Clinical IPD: ↓C3 and ↓C4

Complement System

Classical Pathway:
- Ab-Ag Binding
- C1q
- C1
- C4
- C2
- C4bC2a
- C3 convertase

Alternative Pathway:
- Microbes
- C3b
- Factor H
- C3b
- B
- D
- C3bi
- C4bBP

C5 convertase:
- C3Cb4bC2a
- C3bBbC3b
- C5a
- C5b
- C6, C7, C8, C9
- Terminal Complement Complex

PspC

PspA

C1q

C3a

C5a
Complement Dysregulation

Streptococcus bind both Factor H and C4bBP
1) Evade immune system
2) Functional Factor H deficiency
3) Factor H facilitates bacterial invasion

Binding to *S. pneumoniae* bacteria
**S. pneumoniae invasiveness \( \propto \) Factor H Binding**

**Strains with high Factor H binding**
1) \( \downarrow \text{C3b} \) and \( \uparrow \text{C3bi} \) (\( \downarrow \text{C3b/iC3b} \))
2) \( \downarrow \text{Phagocytosis} \)
3) \( \uparrow \text{Virulence} \)

---

**Graphs**

- **B**: Scatter plot showing the relationship between Factor H binding (FI) and C3b/iC3b deposition (log10 FI). The correlation coefficient \( r_s = -0.76 \) with \( P < 0.0001 \).
- **C**: Box plot comparing Factor H binding (FI) between High (HI) and Weak (WI) Invasive Strains. The difference is significant with \( P = 0.011 \).
Rate SP-HUS Rising

<table>
<thead>
<tr>
<th>England</th>
<th>aHUS / HUS</th>
<th>SP- HUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995-1988</td>
<td>15/288 (5.2%)</td>
<td>0/15</td>
</tr>
<tr>
<td>1997-2001</td>
<td>18/413 (4%)</td>
<td>8/18 (44%)</td>
</tr>
<tr>
<td>New Zealand</td>
<td>19/ (?)</td>
<td>11/19 (58%)</td>
</tr>
</tbody>
</table>

Epidemiology SP-HUS

- Organism
  - Strain-specific characteristics

- Recipient
  - Age-related
  - Clinical risk factors
  - Genetic risk factors

- Bacterial strain
  - ~0.5%

- Clinical factors
- Genetic factors

SP-HUS
Clinical risk factors in SP-HUS

Trends in US Hospital Stays for *Streptococcus pneumoniae* HUS. Vessenmeyer AF, Edmonson MB

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>SP-HUS</th>
<th>no HUS</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 3 yrs</td>
<td>73</td>
<td>43.8</td>
<td>4.4 (2.1-9.5)</td>
</tr>
<tr>
<td>Bacteremia/sepsis</td>
<td>58.6</td>
<td>27.7</td>
<td>3.8 (1.9-7.8)</td>
</tr>
<tr>
<td>Complicated pneumonia*</td>
<td>72%</td>
<td>25%</td>
<td>9.2 (4.1-20.7)</td>
</tr>
</tbody>
</table>

* Empyema, necrotizing pneumonia
Empyema

Pathological Empyema Specimen. Creative Common Licensing From Yale Rosen.

Empyema and atelectasis of the right lower lobe
ID: /4441.jpg

http://www.ultrasoundcases.info
Empyema as risk factor

*Several theories*

- Empyema → more aggressive strain
- Static growth conditions
  - ↑Neuraminidase synthesis
  - ↑ neuraminidase activity
    - (optimum – pH 5.0)
  - ↑autolysin and bacterial cytolysis
- High Dose antibiotics
  - Bacterial killing
Prevnar-7: Heptavalent Pneumococcal Vaccine
Capsular polysaccharides from 7 strains: 4, 6B, 9V, 14, 18C, 19F, 23F

Image download Protein Data Bank (www.rcsb.org/pdb/images)
Crystal structure of diphteria toxin mutant CRM197. Malito et al. PNAS 2012
Correlation Between Prevnar-7 & ↑SP-HUS

Invasive Pneumococcal Disease

↑ other serotypes
**SP-HUS Serotypes post-Prevnar7**

**Majority not covered by Prevnar7**
- High-prevalence of serotype 19, especially after 2003

**Prevnar13** (2010): 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, 23F

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Prevnar-7</th>
<th>England(^a) (98-2005)</th>
<th>North America(^b) (97-2010)</th>
<th>After 2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>19A</td>
<td>No</td>
<td>50%</td>
<td>50%</td>
<td>63-75%</td>
</tr>
<tr>
<td>14</td>
<td>Yes</td>
<td>4%</td>
<td>17%</td>
<td>0-4%</td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td>4%</td>
<td>13%</td>
<td>22%</td>
</tr>
<tr>
<td>7</td>
<td>No</td>
<td>-</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>No</td>
<td>-</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>No</td>
<td>8%</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>No</td>
<td>8%</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>No</td>
<td>-</td>
<td>8%</td>
<td></td>
</tr>
</tbody>
</table>

Data from Waters et al, 2007\(^a\) and Banerjee et al, 2011\(^b\)
Strain differences in *nan* genes

**Japanese Study** (Janapatia 2013)
- Increase in *nanC* genes in SP-HUS and necrotizing pneumonias
- Association with serotype 3

**European Study** (Smith 2013)
33 IPD strains (+ SP-HUS and no SP-HUS)
- No difference in *nanA*, *nanB* or *nanC* enzyme activity
- No difference in *nanA* mRNA level
- No correlation between SP-HUS and *nanA* allelic variants
Genetic Risk Factors

Szilagyi et al (2013): Genetic typing on #5 SP-HUS cases

- 60-65% of aHUS possess genetic risk factors
- 60% SP-HUS *also* have genetic risk factors

<table>
<thead>
<tr>
<th>Genotyping Results</th>
<th>No. (%)</th>
<th>aHUS risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haplotypes</td>
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<td></td>
</tr>
<tr>
<td>CFH H3</td>
<td>1/5 (20%)</td>
<td>Y</td>
</tr>
<tr>
<td>MCPggac</td>
<td>3/5 (60%)</td>
<td>Y</td>
</tr>
<tr>
<td>Mutations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CFH (R1149X)</td>
<td>1/5 (20%)</td>
<td>Novel (Y)</td>
</tr>
<tr>
<td>CFI (P50A)</td>
<td>1/5 (20%)</td>
<td>Y</td>
</tr>
<tr>
<td>Thrombomodulin (T44A)</td>
<td>1/5 (20%)</td>
<td>Novel (Y)</td>
</tr>
<tr>
<td>Anti-Factor H antibodies</td>
<td>0%</td>
<td>Y</td>
</tr>
</tbody>
</table>
Treatment

**Supportive**
- High dose antibiotics
- +/- Renal replacement
- +/- Mechanical ventilation

**Transfusion**
- Variable practices
- No clear evidence for washed RBC, plasma avoidance

**Therapeutic TPE**
- Rare, efficacy unknown
- ? Replacement fluids
- ? Safety issues – age, weight, stability
  - Whole blood exchange versus TPE

ASFA 2015
Moderated Discussion!
Summary

SP-HUS

• Rare, but increasing cause of aHUS
• Younger patients
• IPD with complicated pneumonia
• Involvement complement system
  • Bacterial consumption
  • Dysregulation
  • Genetic predispositions (?)
• ↑ morbidity and morality relative to *E. coli*-HUS